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## A pilot randomized controlled trial with paroxetine for subthreshold PTSD in Operation Enduring Freedom/Operation Iraqi Freedom era veterans

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### Abstract

Subthreshold posttraumatic stress disorder (PTSD) is associated with increased risk for suicidality, depression, and functional impairment. We thus conducted a small ( $N=12$ ) pilot randomized controlled trial (RCT) with paroxetine for subthreshold PTSD in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) era veterans. Hospital Anxiety and Depression Scale (HADS) scores improved by 30.4% in the paroxetine group. Paroxetine may have promise for subthreshold PTSD.

### Keywords

PTSD; Subthreshold; Paroxetine

### 1. Introduction

The specific constellations of symptoms characterizing subthreshold posttraumatic stress disorder (PTSD) have been variously described (Blanchard et al., 1994; Carlier and Gersons, 1995; Marshall et al., 2001, 2001b; Stein et al., 1997; Weiss et al., 1992), but individuals with subthreshold PTSD have generally been characterized as having experienced a traumatic event and subsequently reporting some, *but not all*, symptoms that are consistent with PTSD (i.e. *not* meeting criteria for “full” PTSD). The prevalence of sub-threshold PTSD (sometimes referred to as “partial PTSD”) appears comparable to full PTSD, and converging evidence suggests that subthreshold PTSD conditions are clinically important and associated with social, occupational, and functional impairment (Marshall et al., 2001a,

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**Appendix A. Supporting information:** Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.psychres.2012.11.008>.

2001b; Stein et al., 1997). Individuals with subthreshold PTSD symptoms also appear to be at increased risk for developing comorbid depressive disorders and suicidal ideation (Marshall et al., 2001). Further, Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans with subthreshold PTSD were more likely to report suicidal ideation and hopelessness compared to veterans without PTSD, and there were also no differences in these clinical symptoms between veterans with subthreshold PTSD and veterans meeting full criteria for PTSD (Jakupcak et al., 2011). Moreover, OEF/OIF veterans with subthreshold PTSD report similar elevated incidents of aggression compared to OEF/OIF veterans with full PTSD (Jakupcak et al., 2007). Degree of impairment increases as the number of PTSD symptoms increases (Marshall et al., 2001), and subthreshold PTSD symptoms may progress to full PTSD (Carty et al., 2006). However, even if subthreshold symptoms do not progress to full PTSD, the associated impairment of subthreshold PTSD can be substantial, with significant and prolonged effects (Cukor et al., 2010). The treatment of subthreshold PTSD thus merits further investigation.

No reported pharmacological intervention studies have specifically targeted patients with subthreshold PTSD to date. Investigations in subthreshold PTSD might logically consider an agent with known efficacy for full PTSD, such as paroxetine (Marshall et al., 2001a,b; Tucker et al., 2000), which is FDA-approved for PTSD. We thus conducted a pilot randomized controlled trial (RCT) with paroxetine in US OEF/OIF era veterans meeting criteria for subthreshold PTSD (as defined in Section 2 below). Whereas prior pharmacological investigations have examined the prevention of PTSD symptom development by intervening immediately following trauma exposure (within hours or 1–2 days), or very shortly after trauma exposure (19.8 days; S.D.=5.2, (Shalev et al., 2012)), the current study investigates a pharmacological intervention in veterans who have already developed subthreshold PTSD and who have been symptomatic for several months or longer.

## 2. Methods

### 2.1. Study design

This pilot randomized, placebo-controlled, double-blind, 12-week trial of paroxetine was conducted at the Durham Veterans Affairs Medical Center (Durham VAMC) in Durham, NC ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00560937) number NCT00560937). Patient enrollment occurred from February 2006 through July 2008. This study was approved by the Durham VAMC Institutional Review Board. All patients provided written informed consent.

### 2.2. Participants

OEF/OIF era veterans, between the ages of 18 and 55, who served in the US military since September 11, 2001, and who met criteria for subthreshold PTSD defined as: meeting Criterion A (exposure to a traumatic event) and demonstrating at least one symptom (frequency 1, and intensity 2) in each cluster category (B= re-experiencing, C=avoidance, D=hypervigilance), but not meeting criteria for full PTSD, as determined by the Clinician-Administered PTSD Scale [CAPS], (Blake et al., 1998).

### 2.3. Study drug

Paroxetine was obtained from Andrx Corporation (Davie, Florida) and over-encapsulation and matching placebo identical in appearance was provided by Fisher (Allentown, PA). Study drug was dispensed at each study visit (except screening and final study visits), with flexible dosing as dictated by patient tolerance and clinical response (range 10–40 mg per day).<sup>1</sup>

## 2.4. Study design

A CAPS was administered at each of the seven study visits, in addition to other psychiatric assessments.<sup>2</sup>

## 2.5. Statistical analysis

The primary endpoint was changed in PTSD symptoms from baseline (Week 0) to final assessment (Week 12), as assessed by the CAPS, analyzed by unpaired Student's *t*-tests of the change scores in the placebo group compared to the paroxetine group. Change scores in the secondary endpoints (The Short Post-Traumatic Stress Disorder Rating Interview [SPRINT] and Hospital Anxiety and Depression Scale [HADS], among others) were also analyzed by unpaired Student's *t*-tests of change scores (two-tailed alpha  $P=0.05$  for each statistical test), uncorrected for multiple comparisons in this exploratory pilot study.

## 3. Results

### 3.1. Participant characteristics

Of 44 participants screened, 13 met study criteria and were randomized (one randomized participant never took a single dose of study medication, and was thus not included in analyses). Of 12 participants included in the analyses, five were randomized to paroxetine and seven to placebo. Ten patients completed the entire 12-week study; two patients completed 5 or more weeks but not the entire study (one placebo patient was withdrawn due to non-compliance with study medication, one paroxetine patient discontinued due to scheduling conflicts - data at 5 weeks carried forward for these two patients). Mean age for placebo group was 35.86 years ( $\pm 9.69$  S.D.); mean age for paroxetine group was 39.21 ( $\pm 4.70$  S.D.).<sup>3</sup> Mean final dose in paroxetine group=34 mg/day, range 30–40 mg/day.

### 3.2. Psychiatric symptom assessment following paroxetine or placebo

Mean total CAPS score changes post-treatment compared to baseline were not significantly different in the paroxetine group compared to the placebo group (see Table 1). Mean SPRINT scores improved non-significantly by 43.2% in the paroxetine group (mean change  $-3.8$  points) compared to 21.9% in the placebo group (mean change  $-2.0$  points). Mean total HADS scores improved by 30.4% following treatment with paroxetine (mean total HADS score change =  $-3.40$  points) compared to improvement in HADS scores by 1.7% following treatment with placebo (mean total HADS score change =  $-0.17$  points), unpaired Student's *t*-test of change scores,  $P < 0.065$ .<sup>4</sup>

### 3.3. Side effect profiles in patients randomized to paroxetine and placebo

Paroxetine was generally well-tolerated in OEF/OIF era veterans.<sup>5</sup> No serious adverse events occurred during this study in either group.

## 4. Discussion

This pilot RCT with paroxetine is the first to report results from a pharmacological intervention in subthreshold PTSD. Although changes in PTSD symptoms were not significantly different in the group receiving paroxetine compared to the group randomized to placebo, veterans receiving paroxetine tended to demonstrate an approximately 30%

<sup>1</sup>See Supplementary materials for complete dosing schedule.

<sup>2</sup>See Supplementary materials for schedule of events (Table 2).

<sup>3</sup>See Supplementary materials for additional participant characteristics and results.

<sup>4</sup>See Supplementary Materials for HADS data (Fig. 1).

<sup>5</sup>See Supplementary Materials for a complete list of Adverse Events (Table 3).

greater reduction in anxiety and depression symptoms compared to patients randomized to placebo (as assessed by the HADS). Given high rates of comorbid depression and anxiety in veterans with PTSD, early intervention for subthreshold PTSD symptoms may have potential to reduce commonly co-occurring mood and anxiety symptoms. Our data are the first to suggest the possibility that intervention with a pharmacological agent may reduce symptoms associated with subthreshold PTSD. Importantly, paroxetine was generally well-tolerated in this OEF/OIF era cohort of veterans with subthreshold PTSD. Initial results are promising, demonstrate feasibility, and potentially contribute to a foundation for future hypothesis-testing.

The main limitation of this pilot RCT is very small sample size, and these results will clearly require replication in a larger cohort to determine if preliminary clinical signals are observable in larger investigations. Additionally, results should be interpreted with caution since there was no change in the primary outcome measure (PTSD symptoms as assessed by the CAPS), and since multiple secondary outcome measures were examined (increasing the likelihood of Type I error, as there were no corrections for multiple comparisons in this exploratory pilot RCT). There were also no women among the 12 participants who completed 5 or more weeks of the study, potentially affecting generalizability. Mean CAPS scores in the group randomized to paroxetine were also quite low at baseline, and hence modifications to study entry criteria for future investigations may be warranted to target a population with a greater degree of subthreshold PTSD symptoms (so that clinical change post-intervention could potentially be detected more easily if present). Although results are very preliminary, initial findings exhibit promise and merit additional study.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

- Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Charney DS, Keane TM. Clinician-administered PTSD Scale for DSM-IV. National Center for Posttraumatic Stress Disorder-Behavioral Science Division. 1998
- Blanchard EB, Hickling EJ, Taylor AE, Loos WR, Gerardi RJ. Psychological morbidity associated with motor vehicle accidents. *Behaviour Research and Therapy*. 1994; 32:283–290. [PubMed: 8192626]
- Carlier IV, Gersons BP. Partial posttraumatic stress disorder (PTSD): the issue of psychological scars and the occurrence of PTSD symptoms. *Journal of Nervous and Mental Disease*. 1995; 183:107–109. [PubMed: 7844572]
- Carty J, O'Donnell ML, Creamer M. Delayed-onset PTSD: a prospective study of injury survivors. *Journal of Affective Disorders*. 2006; 90:257–261. [PubMed: 16376993]

- Cukor J, Wyka K, Jayasinghe N, Difede J. The nature and course of subthreshold PTSD. *Journal of Anxiety Disorders*. 2010; 24:918–923. [PubMed: 20655169]
- Jakupcak M, Conybeare D, Phelps L, Hunt S, Holmes HA, Felker B, Klevens M, McFall ME. Anger, hostility, and aggression among Iraq and Afghanistan War veterans reporting PTSD and subthreshold PTSD. *Journal of Traumatic Stress*. 2007; 20:945–954. [PubMed: 18157891]
- Jakupcak M, Hoerster KD, Varra A, Vannoy S, Felker B, Hunt S. Hopelessness and suicidal ideation in Iraq and Afghanistan War Veterans reporting subthreshold and threshold posttraumatic stress disorder. *Journal of Nervous and Mental Disease*. 2011; 199:272–275. [PubMed: 21451353]
- Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *American Journal of Psychiatry*. 2001a; 158:1982–1988. [PubMed: 11729013]
- Marshall RD, Olfson M, Hellman F, Blanco C, Guardino M, Struening EL. Comorbidity, impairment, and suicidality in subthreshold PTSD. *American Journal of Psychiatry*. 2001b; 158:1467–1473. [PubMed: 11532733]
- Shalev AY, Ankri Y, Israeli-Shalev Y, Peleg T, Adessky R, Freedman S. Prevention of posttraumatic stress disorder by early treatment: results from the jerusalem trauma outreach and prevention study. *Archives of General Psychiatry*. 2012; 69:166–176. [PubMed: 21969418]
- Stein MB, Walker JR, Hazen AL, Forde DR. Full and partial posttraumatic stress disorder: findings from a community survey. *American Journal of Psychiatry*. 1997; 154:1114–1119. [PubMed: 9247398]
- Tucker P, Smith KL, Marx B, Jones D, Miranda R, Lensgraf J. Fluvoxamine reduces physiologic reactivity to trauma scripts in posttraumatic stress disorder. *Journal of Clinical Psychopharmacology*. 2000; 20:367–372. [PubMed: 10831026]
- Weiss DS, Marmar CR, Schlenger WE, Fairbank JA, Jordan BK, Hough RL. The prevalence of lifetime and partial post-traumatic stress disorder in Vietnam theater veterans. *Journal of Traumatic Stress*. 1992; 5:365–376.

**Table 1**  
**Psychiatric Rating Scales in OEF/OIF Era Veterans with Subthreshold PTSD**

Group	Assessment measure	Week 0 Mean $\pm$ (SD)	Week 12 Mean $\pm$ (SD)	Change score
Paroxetine	CAPS total	19.00 (8.46)	15.60 (5.98)	-3.40 (7.37)
	SPRINT	8.80 (6.57)	5.00 (4.69)	-3.80 (6.14)
	HADS total	11.20 (5.76)	7.80 (3.70)	-3.40 (2.70)
	CD-RISC	73.80 (15.02)	74.60 (20.28)	-0.80 (11.67)
Placebo	CAPS total	26.42 (12.09)	21.42 (7.89)	-5.00 (6.78)
	SPRINT	9.14 (6.18)	7.14 (5.87)	-2.00 (1.15)
	HADS total	10.00 (5.76)	9.83 (5.12)	-0.17 (1.80)
	CD-RISC	80.57 (16.28)	79.28 (12.12)	-1.29 (9.86)